Information Disclosure Statement

The record is very confusing as to whether or not an Information Disclosure Statement has been filed in this application, although the examiner references such a filing (without enclosures or PTO 1449 forms) and has marked up an attached. A Supplemental Information Disclosure Statement was mailed December 3, 1998, enclosing the Search Report in the corresponding PCT application. A complete copy of the Information Disclosure Statement that is referred to by the Examiner, copies of the references cited therein, and the PTO 1449 forms, will be submitted under separate cover to eliminate any confusion on this point.

Restriction Requirement and Election of Species

As discussed at the interview, applicants have elected one group of claims to prosecute, as well as elected the species of lupus and a defined peptide, with the understanding that the generic claims will be examined if claims to the species are determined to be patentable. As discussed, although the claims are drawn to different chemical entities, they are being selected based on common mechanisms of action, and as such are species, not separate inventions.

Priority Claim

As also discussed at the interview, the complete claims to priority are defined in the application at page 1, lines 5-12, and the Declaration of Inventorship. Priority is not claimed to any other applications, even though there are related applications to which one of these applications claims priority.

Rejections under 35 U.S.C. §112

Claims 1-5 and 11-18 were rejected under 35 U.S.C. §112 as indefinite and lack of enablement. These rejections are respectfully traversed if applied to the amended claims.

Composition claims 1-5 have been amended to refer to an immunogenic composition, rather than a vaccine, as suggested by the Examiner. The effective amount has been defined by reference to alleviation of symptoms (referred to as "manifestations" at page 9, line 17; "symptoms" at page 50, lines 5-7) of disorders caused by Epstein-Barr virus, rather than to preventing or alleviating the disease *per se*. As discussed at the interview, autoimmune disorders such as lupus are characterized by symptoms, which can vary widely in severity, frequency, and onset. The EBV compositions have also been defind as modified so that vaccine is not itself capable of inducing disease (see page 8, lines 32-35; page 19, line 28-page 20, line 7.

It is believed these amendments adequately respond to the issues raised by the examiner regarding indefiniteness. With regard to the "at risk" language and what criteria would be measured, it is believed that these factors are well known to those skilled in the field of treating autoimmune disorders. For example, it is well known that individuals at risk can be assessed by virtue of family studies or genetic analysis (for example, see discussion re genetics at pages 31 of application), age; sex, and ethnic background (for example, it is well established that lupus is more common in young female adults than in other groups); and other factors. It is equally well known that certain symptoms can be assessed to diagnose autoimmune disease, as well as its severity. An example is by measurement of autoantibodies (see page 12, for example, and

Example 1 beginning at page 27.)

At the interview, the complexity of these diseases was discussed and acknowledged, as well as the difficulty in providing human clinical data at this stage in the development of the invention, particularly when the inventors are doing their research at a non-profit institution. the deficiency, according to the examiner, in the data presented in the application, was not that the specification did not teach how to make the claimed compositions, nor that the applicants had demonstrated their ability to *induce* autoimmunity, but that the data failed to prove the efficacy of the composition and method of use thereof in treating a disease.

Enclosed in response is a Declaration by Dr. Harley that demonstrates (1) that the mechanisms described with reference to lupus are also involved in a totally distinct autoimmune disorder, rheumatoid arthritis, and (2) that compositions as defined by the claims can be used to induce tolerance in an animal which in controlled studies (see application at page 30, "Rabbits immunized with PPPGMRPP developed antibody beyond the peptide of immunization which bound to many other octapeptides in the spliceosome, antinuclear autoantibodies, anti-double stranded DNA autoantibodies and clinical features that suggests the illness known in man as systemic lupus erythematosus".) This further supports the mechanisms and supporting data in the application (see especially example 7, beginning at page 42) showing the association between EBV infection and development of lupus, and how the incidence of autoimmune disease is lower in those who have not been infected with EBV.

Rejections under 35 U.S.C. §102(b), 102(e) or 103

Claims 1-5 and 11-16 were rejected under 35 U.S.C. §102(b), 102(e) or 103. Claims 1, 2, 3, 5, 11, 12, 13, and 16 were rejected under §102(b) as disclosed by U.S. Patent No. 4,707,358 to Kieff; claims 1, 2, 3, 5, 11, 12, 13 and 16 were rejected under §102(e) over U.S. Patent No. 5,726,286 to Alderson; claims 1, 2, 3, 5, 11, 12, 13 and 16 were rejected under §102(e) as disclosed by U.S. Patent No. 5,679,774 to Wolf. Claims 1-5, 11, 12, 13, 14 and 16 were rejected under §102(b) as disclosed by U.S. Patent No. 4,654,419 to Vaughan. Claims 14, 15, 17 and 18 were rejected under 35 U.S.C. §103 over U.S. Patent No. 4,654,419 to Vaughan in combination with Harley and James, J. Lab. Clin. Med. 126(6), 509-516 (1995). These rejections are respectfully traversed if applied to the amended claims.

None of the prior art discloses EBV compositions which have been modified to remove structures which elicit an autoimmune reaction since none of the prior art recognizes (1) EBV can elicit an autoimmune reaction or (2) which portions of the EBV causes a problem and therefore there is no motivation to make such a modified EBV composition nor an enabling disclosure to do so.

Kieff

Kieff discloses DNA encoding EBV proteins, and recombinant proteins which are useful in vaccines against EBV infection. There is nothing with regard to a role of EBV in autoimmunity, a recognition that certain structures in the viral proteins elicit an autoimmune response, how to identify such structures (and thereby know to remove and/or alter them).

Therefore, Kief neither discloses nor makes obvious the claimed compositions and methods of use.

Alderson

Alderson discloses isolated EBV proteins which allegedly inhibit binding of the virus to the MHCII receptor and thereby prevent viral infection. There is nothing with regard to reducing autoimmunogenicity of the viral proteins, nor a method to prevent or decrease symptoms associated with autoimmune disease, although there is some speculation that the peptides are useful in suppressing immune response, presumably T cell mediated (rather than humoral) immune responses, by virtue of binding to the MHC II receptor.

Wolf

Wolf discloses EBV proteins and fusion proteins. There is no disclosure of modifications of any of the naturally occurring proteins to reduce the liklihood they could induce autoimmunity. The only methods of use which are taught use the unmodified recombinant proteins (i.e., not modified to reduce autoimmunogenicity) to prevent a viral infection.

Vaughan

Vaughan discloses Epstein-Barr virus nuclear antigen. Of the examples provided, all contain the peptides applicants have identified as immunoreactive 9see, for example, graphs 7 and 8A-E, referenced at pages 11 and pages 46-49, Example 8, Table 5).

Harley and James

This application claims priority to U.S. Serial No. 08/160,604. The disclosure of the

1995 Harley and James paper, which discloses the EBV compositions that can be used to elicit an autoimmune disorder in an animal, and which are preferentially removed in the claimed method and compositions, as first disclosed in the provisional application 60/019,053, is present in the earlier filed application. It should therefore not be available as prior art. However, even it is, there is no teaching that says one should combine peptides identified by Harley and James as eliciting an autoimmune reaction with the vaccines against EBV infection of Vaughan, incorporating viral proteins (EBNA) which were not identified by Harley and James as eliciting autoimmunogenicity.

In summary, none of the prior art discloses nor makes obvious the subject matter of the claims as amended. All claims 1-5 and 11-18 as pending upon entry of this amendment are attached in an Appendix to facilitate review by the Examiner. Allowance of all claims is earnestly solicited.

Respectfully submitted,

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APPENDIX: Claims as amended.

1. (amended) [A vaccine] An immunogenic composition for alleviating or preventing symptoms of autoimmune disorders induced by infection with Epstein-Barr virus comprising

a modified Epstein-Barr virus or a modified component thereof, wherein one or more structures of the Epstein-Barr virus are removed or altered to decrease the potential that the vaccine will induce an autoimmune disorder, in a pharmaceutically acceptable carrier for administration of the virus or viral component in an amount and mode of administration effective to alleviate or prevent symptoms associated with the autoimmune disorders.

2. (amended) The [vaccine] composition of claim 1 [wherein one or more structures of the Epstein-Barr virus are removed or altered to decrease the potential that the vaccine will induce an autoimmune disorder] comprising modified Epstein-Barr virus components.

3. (amended) The [vaccine] composition of claim 1 wherein the component of Epstein-Barr virus is selected from the group consisting of peptides or proteins expressed from recombinant DNA or RNA with sequence identity to Epstein-Barr virus, viral DNA or RNA, and carbohydrate components of the Epstein-Barr virus.

4. (twice amended) The [vaccine] composition of claim 1 wherein the Epstein-Barr virus comprises the nuclear antigen 1 protein not including a peptide sequence selected from the group consisting of PPPGRRP, GRGRGRGG and RGRGREK.

5. (amended) The [vaccine] composition of claim 1 in a pharmaceutical carrier for administration by injection.

11. (amended) A method for preventing or alleviating autoimmune disorders induced by infection with Epstein-Barr virus comprising

[vaccinating or] administering to a individual at risk of developing, or who has been identified as having symptoms associated with, an autoimmune disorder induced by infection with Epstein-Barr virus,

a composition comprising a killed or attenuated Epstein-Barr virus or a component thereof, or modifications thereof wherein one or more structures of the Epstein-Barr virus are removed or altered to decrease the potential that the vaccine will induce an autoimmune disorder, in a pharmaceutically acceptable carrier for administration of the virus or viral component in an amount and mode of administration effective to alleviate or prevent the autoimmune disorders.

12. (amended) The method of claim 11 wherein [one or more structures of the Epstein-Barr virus are removed or altered to decrease the potential that the vaccine will induce an autoimmune disorder] the composition comprises modified Epstein-Barr virus components.

13. The method of claim 11 wherein the component of Epstein-Barr virus is selected from the group consisting of peptides or proteins expressed from recombinant DNA or RNA with sequence identity to Epstein-Barr virus, viral DNA or RNA, and carbohydrate components of the Epstein-Barr virus.

14. (amended) The method of claim 11 wherein the Epstein-Barr virus comprises the nuclear

antigen 1 protein not including a peptide sequence selected from the group consisting of PPPGRRP (SEQ ID NO:1), GRGRGRGG (SEQ ID NO:2) and RGRGREK (SEQ ID NO:3).
15. (amended) The method of claim 11 wherein the individual has symptoms of or is at risk of developing an autoimmune disorder selected from the group consisting of systemic lupus erythematosus, Sjogren's syndrome, rheumatoid arthritis, juvenile onset diabetes mellitus, Wegener's granulomatosis, inflammatory bowel disease, polymyositis, dermatomyositis, multiple endocrine failure, Schmidt's syndrome, autoimmune uveitis, Addison's disease, adrenalitis, primary biliary cirrhosis, Graves' disease, thyroiditis, Hashimoto's thyroiditis, autoimmune thyroid disease, pernicious anemia, lupoid hepatitis, demyelating diseases, multiple sclerosis, subacute cutaneous lupus erythematosus, hypoparathyroidism, Dressler's syndrome, myasthenia gravis, autoimmune thrombocytopenia, idiopathic thrombocytopenic purpura, hemolytic anemia, autoimmune hemolytic anemia, pemphigus vulgaris, pemphigus, bullous pemphigoid, dermatitis herpetiformis, alopecia areata, autoimmune cystitis, pemphigoid, scleroderma, progressive systemic sclerosis, CREST syndrome (calcinosis, Raynaud's esophageal dysmotility, sclerodactyly, and telangiectasia), adult onset diabetes mellitus (Type II diabetes), male or female autoimmune infertility, ankylosing spondylitis, ulcerative colitis, Crohn's disease, mixed connective tissue disease, polyarteritis nodosa, systemic necrotizing vasculitis, juvenile onset rheumatoid arthritis, glomerulonephritis, atopic dermatitis, atopic rhinitis, Goodpasture's syndrome, Chagas' disease, sarcoidosis, rheumatic fever, asthma, recurrent abortion, anti-phospholipid syndrome, farmer's lung, erythema multiforme, postcardotomy syndrome, Cushing's syndrome, autoimmune chronic active hepatitis, bird-fancier's lung, allergic encephalomyelitis, toxic necrodermal lysis, alopecia, Alport's syndrome, alveolitis, allergic alveolitis, fibrosing alveolitis, interstitial lung disease, erythema nodosum, pyoderma gangrenosum, transfusion reaction, chronic fatigue syndrome, fibromyalgia, Takayasu's arteritis, Kawasaki's disease, polymyalgia rheumatica, temporal arteritis, giant cell arteritis, Sampter's syndrome (triaditis also called, nasal polyps, eosinophilia, and asthma), Behcet's disease, Caplan's syndrome, dengue, encephalomyositis, endocarditis, myocarditis, endomyocardial fibrosis, endophthalmitis, erythema elevatum et diutinum, psoriasis, erythroblastosis fetalis, fascitis with eosinophilia, Shulman's syndrome, Felty's syndrome, filariasis, cyclitis, chronic cyclitis, heterochromic cyclitis, Fuch's cyclitis, IgA nephropathy, Henoch-Schonlein purpura, glomerulonephritis, cardiomyopathy, post vaccination syndromes, Hodgkin's and non-Hodgkin's lymphoma, renal cell carcinoma, Eaton-Lambert syndrome, relapsing polychondritis.
16. (amended) The method of claim 11 wherein the vaccine is administered prior to infection with Epstein-Barr virus.
17. (amended) The method of claim 11 wherein the vaccine is administered to an individual who has or has previously had an infection with Epstein-Barr virus.
18. (amended) The method of claim 11 wherein the autoimmune disorder is systemic lupus erythematosus.